UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,173	07/12/2001	Jay M. Short	09010-017006	3152

20985 7590 06/17/2003

FISH & RICHARDSON, PC
4350 LA JOLLA VILLAGE DRIVE
SUITE 500
SAN DIEGO, CA 92122

EXAMINER
SLOBODYANSKY, ELIZABETH

ART UNIT	PAPER NUMBER
1652	15

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/905,173	Applicant(s) SHORT ET AL.	
	Examiner Elizabeth Slobodyansky	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-55,93 and 94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-55,93 and 94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 12
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed January 22, 2003 amending the specification to correct clerical errors in the reference to the parent applications has been entered.

The amendment filed March 25, 2003 (Paper No. 14) canceling claims 1-41 and 56-92 and adding claims 93-94 has been entered.

Claims 42-55, 93 and 94 are pending and under consideration.

Election/Restrictions

Applicant's election with traverse of Group IV, Claims 42-55, as drawn to a method of generating a variant of a polynucleotide of SEQ ID NO:23, in Paper No. 14, page 6, is acknowledged. The traversal is on the ground(s) that SEQ ID NOs: 17, 18, 19, 20, 23 and 39 encode "all transaminases originally derived from organism *Aquifex*" (page 6). Further, "Applicants respectfully request that SEQ ID NOS: 17, 18, 19, 20, 22 and 39 be examined with SEQ ID NO:23. The sequences requested to be examined are less in number than the 10 individual independent and distinct nucleotides sequences the Patent Office has determined to be a reasonable number to be examined in a single application" (page 7). Applicants traversal is not found persuasive for the following reasons: the identical source such as originating from *Aquifex*, does not translate into identical structure and utility. While the above sequences encode transaminases, these transaminases are, in fact, different enzymes catalyzing different

reactions and having different structures. Further, Applicant is reminded that the MPEP recites **up to 10** distinct nucleotide sequences not **at least 10** nucleotide sequences, and while applicants assert that they are claiming less than 10 independent and distinct sequences, they are in fact claiming many more than 10 independent and distinct sequences when one considers they are claiming each of SEQ ID NOS: 17, 18, 19, 20, 22 and 39 as well as those which encode SEQ ID NOs: 25, 26, 27, 28, 30, 31 and 40 as well as those which are "substantially identical thereto".Thus, applicants are claiming many more than 10 independent and distinct sequences. Thus these inventions are distinct for the reasons given previously. *"For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP 808.02."* (see MPEP 803).

The requirement is still deemed proper and is therefore made FINAL.

Claims 42-55, 93 and 94 have only been examined with respect to SEQ ID NO:23 or a polynucleotide encoding SEQ ID NO:31.

Information Disclosure Statement

As part of the information disclosure statement filed July 12, 2001, Applicants provided form PTO-892 and initialed and signed form PTO-1449 from the earlier filed

applications. These forms are lined through as the examiner can not initial and sign them unless the information is resubmitted on a clean form PTO-1449.

The single citation is lined through on otherwise initialed and signed "Page 1" of form PTO-1449 because it is incomplete and does not contain sufficient information to identify the reference.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (for example, page 61). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The disclosure is objected to because of the following:

On page 6 Applicants recite "(SEQ ID NO:29) of *Aquifex degensii* ..." (emphasis added).

On page 74 Applicants recite "Histadine-phosphate Aminotransferase". On page 75 Applicants recite "hp aminotransferase". "hp" should be written out.

Appropriate correction is required.

The specification is confusing as providing two different definitions of "substantially identical" in relation to amino acid sequences. On page 11, paragraph 0058, Applicants recite "The phrase "substantially identical" in the context of two nucleic acids or polypeptides" (emphasis added). And further an additional definition of "a "substantially identical" amino acid sequence" is given (pages 11-12, paragraph 0059).

Clarification is required.

The specification recites "GSSM" (for example, on page 13). It is suggested that the first time an abbreviation is used for a term that is not widely known in the art, that the abbreviated term be written out in full (gene site saturated mutagenesis), followed by its abbreviation in parenthesis.

Appropriate correction is required.

Claim Objections

Claims 43, 49 and 94 are objected to because of the following informalities:

Claims 43, 49 and 94 recite "in viva mutagenesis" where in appears "in vivo mutagenesis" is intended.

Appropriate correction is required.

Claims 42-55, 93 and 94 are objected to under 37 CFR 1.75(d)(1) as being in improper form because the claim states an improper Markush group. Compounds included within a Markush group must (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility (See MPEP 803.02.) While the different polynucleotides recited in claims 42-55, 93 and 94 may encode transaminases, these transaminases are, in fact, different enzymes having different utilities (for example, pages 6-7 and 73-75). Furthermore, even considering transaminases as having a common utility, the specification does NOT disclose that the compounds share a substantial structural feature disclosed as being essential to that utility. Because a substantial structural feature is not disclosed as being essential to the utility that is common to the recited polynucleotides, the claims state an improper Markush group.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-55, 93 and 84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of generating a variant of a nucleic acid comprising modifying, deleting or adding one or more nucleotides in the sequence of said nucleic acid. Since the number of possible modifications is not limited, the claims are drawn to a method of generating a variant of a nucleic acid of unknown structure. In addition, the function of a variant is not limited either.

Therefore, the claims are drawn to a method of generating a genus of variants of any structure and function. Said genus encompasses an unlimited number of nucleic acids. The specification teaches the structure of only a single representative species of such nucleic acids, i.e., that of SEQ ID NO:23 encoding histidinol phosphate aminotransferase (page 74). Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties and/or fails to describe the correlation between structure and function common to all members of the genus. Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42-55, 93 and 94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 42 (claims 43-55 dependent thereon) is indefinite in the recitation of "obtaining a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOS: 17, 18, 19, 20, 22, 23, and 39, sequences substantially identical thereto, sequences complementary thereto, fragments comprising at least 30 consecutive nucleotides thereof, and fragments comprising at least 30 consecutive nucleotides of the sequences complementary to SEQ ID NOS: 17, 18, 19, 20, 22, 23, and 39" for the following reasons.

The claim is indefinite in the recitation of "sequences complementary thereto" as it is unclear if the term "thereto" refers to SEQ ID NOS: 17, 18, 19, 20, 22, 23, or 39 or "the substantially identical" sequence. The claim is also indefinite in the recitation of "fragments comprising... thereof" as it is unclear which nucleic acids are being referred to by the term "thereof". The term "substantially identical" in regard to nucleic acid sequences is not clearly defined in the specification (page 11). While the specification refers to at least 50% identity between two sequences, the span over which such identity occurs is defined by non-limiting examples. The specification teaches that

"Typically, the substantial identity exists over a region of at least about 100 residues" (page 11, emphasis added).

In this Office action, the claim will be interpreted as being drawn to a method of generating a variant comprising obtaining a nucleic acid selected from the group consisting of (a) the polynucleotide of SEQ ID NOS:17, 18, 19, 20, 22, 23, or 39, (b) any polynucleotide having at least 50% sequence identity to any fragment of the polynucleotide of SEQ ID NOs:17, 18, 19, 20, 22, 23, or 39, (c) any polynucleotide which is completely complementary to (a) or (b), (d) a fragment of at least 30 consecutive nucleotides of (a), (b), or (c).

Claim 93 (claim 94 dependent thereon) is indefinite for similar reasons. In addition claim 93 is indefinite as reciting "the sequences complementary to SEQ ID NOS: 25, 26, 27, 28, 30, 31 and 40" wherein said sequences are the amino acid sequences. It is unclear what the term "complementary" means in relation to amino acid sequences.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 42 and 93 are rejected under 35 U.S.C. 102(b) as being by Henner et al.

Henner et al. teach the nucleotide sequence of *Bacillus subtilis* hisH gene within the trp operon (Figure 1). The sequence of HisH gene is at least 50% identical to a fragment of least 30 or 100 nucleotides of SEQ ID NO:23. Henner et al. teach the use of integrative plasmids to produce variant hisH gene with deletions and insertions (Figure 2, Table 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 42-55, 93 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henner et al. in view of Short (US Patent 5,939,250).

Claims 42 and 93 are included in this 103 rejection to the extent that they clearly encompass the methods with the limitations of claims 43-55 and 94, wherein said modifications are introduced by the specifically claimed methods. These particular embodiments of claims 42 and 93 are not anticipated although as discussed above, claims 42 and 93 also embrace embodiments which are anticipated. Thus both the 102 and 103 rejections are proper.

The teachings of Henner et al. are outlined above. Henner et al. do not use the methods of mutagenesis specifically recited in Claims 43-55 and 94 to produce a variant.

Short teaches a number of known techniques for directed mutagenesis for the development of variant nucleic acids. Short specifically teaches "error-prone PCR", "shuffling", "oligonucleotide-directed mutagenesis", "assembly PCR", "sexual PCR mutagenesis", "in vivo mutagenesis", "cassette mutagenesis", "recursive ensemble mutagenesis", "exponential ensemble mutagenesis", "site-specific mutagenesis", "gene reassembly", and "gene site saturated mutagenesis".

One of ordinary skill in the art at the time of filing would have been motivated to modify the nucleic acid sequence hisH gene taught by Henner et al. using each of the methods taught by Short, including "error-prone PCR", "shuffling", "oligonucleotide-directed mutagenesis", "assembly PCR", "sexual PCR mutagenesis", "in vivo mutagenesis", "cassette mutagenesis", "recursive ensemble mutagenesis", "exponential

ensemble mutagenesis","site-specific mutagenesis", "gene reassembly", "gene site saturated mutagenesis", in order to identify the role of hisH gene in the *Bacillus subtilis trp* operon and metabolism. One of ordinary skill in the art at the time of filing would have a reasonable expectation of success because of the high level of knowledge in the field of nucleic acid mutagenesis and the teachings of Henner et al. who successfully generated a variant of hisH gene using plasmids interrupting the promoter region thereof. Thus Henner et al. and Short make obvious claims 42-55, 93 and 94 drawn to methods of generating a variant of a nucleic acid comprising a sequence substantially identical to SEQ ID NO: 23 and modifying, deleting or adding one or more nucleotides in said sequence to another nucleotide, wherein the modifications are introduced by error-prone PCR (claims 43,44 and 94), shuffling (claims 43, 45 and 94), oligonucleotide-directed mutagenesis (claims 43, 46 and 94), assembly PCR (claims 43, 47 and 94), sexual PCR mutagenesis (claims 43, 48 and 94), in vivo mutagenesis (claims 43, 49 and 94), cassette mutagenesis (claims 43, 50 and 94), recursive ensemble mutagenesis (claims 43, 51 and 94), exponential ensemble mutagenesis (claims 43, 52 and 94), site-specific mutagenesis (claims 43, 53 and 94), gene reassembly (claims 43, 54 and 94), or gene site saturated mutagenesis (claims 43, 55 and 94).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

June 12, 2003